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Clinical Notes

False-positive results in SARS-CoV-2 antigen test with rhinovirus-A infection

Shogo Otake,[1] Sonoko Miyamoto,[2] Ai Mori,[2] Tomotada Iwamoto[2] and Masashi Kasai[1]

[1]*Division of Infectious Disease, Department of Pediatrics, Hyogo Prefectural Kobe Children's Hospital,* [2]*Department of Infectious Diseases, Kobe Institute of Health, Kobe, Japan*

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Since the outbreak of coronavirus disease-2019 (COVID-19) in December 2019, more than 40 million people have been infected and more than 1 million have died. In Japan, approximately 80 000 people have been infected.[1] The gold standard for testing is the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA through reverse transcriptase polymerase chain reaction (RT-PCR).[2] However, only a few facilities perform RT-PCR testing, while others alternatively perform the antigen test. Espline SARS-CoV-2 (Fujirebio, Tokyo, Japan) is a SARS-CoV-2 antigen detection test in which the nasopharyngeal swab is obtained and tested by immunochromatography based on enzyme immune response.[2] According to the clinical guidelines in Japan, patients with positive rapid antigen results are declared COVID-19 positive.[2] The rapid antigen test was introduced for the benefit of obtaining results easily and quickly. We performed multiplex PCR using a FilmArray Respiratory Panel 2.1 (FilmArray; Bio Mérieux, Marcy-l'Etoile, France) for the patients who tested positive through the rapid antigen test. FilmArray Respiratory Panel 2 demonstrated a positive agreement of 91.7% and a negative agreement of 93.8% based on FilmArray Respiratory Panel or two PCR assays targeting *IS1001* for *Bordetella parapertussis*, followed by bidirectional sequencing.[3] FilmArray can detect 21 microorganisms simultaneously, including the SARS-CoV-2. Here we report three cases of human rhinovirus A (HRV-A) infection where the patients presented with false-positive results for SARS-CoV-2 on the rapid antigen test.

Table 1 shows the three cases. Case 1 was a 3-year-old boy with trisomy 13, who was admitted to the hospital because of fever, cough, and hypoxemia. Case 2 was a 2-year-old girl with central hypoventilation syndrome, who presented with fever and rhinorrhea, and convulsions due to hyponatremia. Case 3 was a 17-year-old girl admitted due to hypoxemia, with a history of surgery for congenital heart disease. None of these patients came in contact with COVID-19 patients. We determined their SARS-CoV-2 on rapid antigen test results to be positive for SARS-CoV-2 because both the reference lines and test lines appeared within 30 min after testing at admission. However, FilmArray detected HRV/enterovirus and not SARS-CoV-2. We extracted viral RNA from nasopharyngeal swabs and performed RT-PCR and DNA sequencing to identify the type of enterovirus. In all three cases, we detected HRV-A, not SARS-CoV-2.

From our cases, we have two clinically important suggestions. First, since false positives have a large impact, patients should be selected not only for symptoms but also for a history of close contact with COVID-19 patients, especially in children. A systematic review of 7,780 pediatric COVID-19 patients reported that 19.3% were asymptomatic.[4] Even in symptomatic patients, there were many nonspecific symptoms such as fever (59.1%) and cough (55.9%).[4] In addition, 5.6% of the cases were co-infected with other viral infections.[4] In this systematic review, 75.6% of patients were exposed to the infection from the family.[4] A history of contact with COVID-19 patients affects the pretest probability more than clinical symptoms only when the risk of social exposure is low. False positives have a large impact on the patient in terms of physical, mental, and financial burden because persons diagnosed with COVID-19 in Japan must be hospitalized.[2]

Second, we should reconfirm through the RT-PCR test when Espline SARS-CoV-2 is positive at the current epidemic level in Japan. In Japan, even if the rapid antigen test result for symptomatic patients is positive, the causative organism could be more common viruses, including HRV, and the rapid test result could be false positive. No false-positive results for Espline SARS-CoV-2 have been reported owing to cross-reactivity with HRV. In other countries, cross-reactivity between SARS-CoV-2 antigens and other infectious diseases such as other coronaviruses, influenza virus, and *Mycoplasma pneumoniae* has been reported.[5] The possible reasons for false-positive results could be low prevalence of the disease in Japan and influence of the test kit. The lower the prevalence is the higher the false positive

Correspondence: Shogo Otake, MD, Hyogo Prefectural Kobe Children's Hospital, 1-6-7, Minato-Jima Minami-Machi, Kobe-shi Chuo-Ku, Hyogo 650-0047, Japan. Email: shogo.ohtake@gmail.com

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Table 1 Three cases with false-positive results in SARS-CoV-2 rapid antigen tests

	Case 1; 3-year-old boy	Case 2; 2-year-old girl	Case 3; 17-year-old girl
Diagnosis	Acute bronchiolitis	Hyponatremia	Acute pneumoniae
Symptoms	Fever, cough, hypoxemia	Fever, nasal discharge, convulsion	Sore throat, cough, hypoxemia
Underlying diseases	Trisomy 13, very- low birthweight infant, laryngomalacia, post tracheostomy	Central hypoventilation syndrome, central diabetes insipidus, post tracheostomy	Congenital cardiac disease (corrected transposition of great arteries, atrioventricular septal defect)
A history of close contact with COVID-19 patients	None	None	None
Inspection day			
Espline SARS-CoV-2	Day 6	Day 8	Day 2
FilmArray Respiratory Panel 2.1	Day 7	Day 9	Day 2
Production lot number of Espline SARS-CoV-2	K4B-039	K4B-039	K4B-019, K4B-039
Results of FilmArray Respiratory Panel 2.1	Human rhinovirus/enterovirus	Human rhinovirus/enterovirus	Human rhinovirus/enterovirus
Type of enterovirus	Human rhinovirus A85	Human rhinovirus A82	Human rhinovirus A11

rate of the test becomes. However, Kobe city has a large number of COVID-19 patients in Japan. Additionally, since the three patients were tested with a kit of the same production lot number (K4B-039), false-positive results may be possible. However, when re-examined using a kit with a different production lot number (K4B-019), the result was again positive in Case 3.

Thus, the indications for rapid antigen tests should be reconsidered, especially in children without any history of the contact with COVID-19 patients. Reconfirmation is warranted through the RT-PCR test when Espline SARS-CoV-2 is positive at the current epidemic level in Japan.

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Disclosure

The authors declare no conflicts of interest.

Author contributions

S.O. wrote the manuscript; A.M. and M.K. provided conceptual advice; S.M., A.M., and T.I. provided technical support, and collected and analyzed data. All authors have read and approved the final manuscript.

Informed consent

We obtained informed consent from the patients' parents to publish this case report.

References

1 World Health Organization. *Coronavirus disease (COVID-19) pandemic. who.int* [homepage on the internet] Genève: World Health Organization. [Cited 2020 Oct 21]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

2 Ministry of Health, Labor and Welfare. *Clinical Management of Patients with COVID-19 A guide for front-line healthcare workers Version 3. mhlw.go.jp* [homepage on the internet]. Tokyo: Ministry of Health, Labor and Welfare. [Cited 2020 Oct 5]. Available from: https://www.mhlw.go.jp/content/000668291.pdf

3 Leber AL, Everhart K, Daly JA *et al*. Multicenter evaluation of BioFire FilmArray respiratory panel 2 for detection of viruses and bacteria in nasopharyngeal swab samples. *J. Clin. Microbiol.* 2018; **56**(6): 1–11.

4 Hoang A, Chorath K, Moreira A *et al*. COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine* 2020; **24**: 100433.

5 Deeks JJ, Dinnes J, Takwoingi Y *et al*. Antibody tests for identification of current and past infection with SARS-CoV-2 (Review). *Cochrane Database Syst. Rev.* 2020; **2**(6): 1–306.